REMARKS

New claims 20-22 have been presented to remove the alternative language from the preamble of claim 5. Support for the new claims 20-22 may be found in previously-presented claim 1 and on page 12, where "prolongation of survival" is discussed in the data for the rat heart transplant model. Accordingly, no new matter has been added by way of these new claims.

35 U.S.C. §112 Rejection

The Office maintains the rejection of the claims as non-enabled, stating that the term "prophylaxis" renders this claim non-enabled.

In no way do Applicants agree with this rejection – especially given the clear supportive documentation provided with the previous response that shows that that the term "prophylaxis" is used in the transplant community to reflect the desire of the transplant clinician to avoid transplant rejection. The Office equates terms such as "prophylaxis" and "prevention" to be absolute – regardless of the way these terms are used in the relevant field (transplant) and regardless of how Applicants have used these terms in the instant application. This is clearly in contravention of the MPEP and the relevant case law, and appears to be the implementation of an Office policy, rather than an analysis of the instant claims and application. However, in order to speed prosecution, Applicants have amended the claims to recite "treatment", which Applicants intend to mean the use of the recited methods in the customary and conventional way transplant clinicians would use such methods to address a transplant scenario. [1]

Given that the offending terms have been removed from the instantly-pending claims, Applicants respectfully submit that the claims are enabled and request withdrawal of the 35 U.S.C. §112, enablement rejection of the pending claims.

35 U.S.C. §103 Rejection

The Examiner has again rejected the previously-pending claims under 35 U.S.C. §103(a) as unpatentable over Heath in view of Albert, further in views of Goekjian et al. (all of record). For the following reasons, the rejection is respectfully traversed.

[1] These conventional uses are exemplified, e.g., in the approved label for Neoral®, the approved label for Simulect®, and the approved label for Rapamune®.

The Office's argument is that Heath provides the two indolymaleimide derivative PKC beta inhibitors identified in Applicants' claims, Goekjian teaches that a PKC beta inhibitor can be used to treat graft vs host disease (GVHD) and Albert teaches that certain other indolymaleimide derivatives that inhibit PKC can be used to treat "T-cell mediate acute or chronic inflammatory disease or disorders, autoimmune disease, graft rejection or cancer." (Office Action at pages 3-4). This Office's argument, in general, is one of equivalency, which is outlined in MPEP 2144.06, which states:

> In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents.

Therefore, for the Office's argument to be proper, the Office must establish that the PKC beta inhibiting compounds of Heath were known prior to Applicant filing date to be equivalent to the compounds of Albert, such that one might select a Heath compound for use in an Albert method.

The Office alleges that Goekjian teaches a PKC beta inhibitor for use in GVHD, and therefore one would substitute a PKC beta inhibitor of Heath into treatment of a disorder of Albert, e.g., transplant rejection. In the July 1, 2009 Office Action on page 2, the Office states that "graft-versus-host disease (GVDH) is not necessarily the same as transplant rejection. As mentioned previously, GVHD can affect almost any organ in the body, and it often mimics autoimmune diseases such as Sjorgren's syndrome, rheumatoid arthritis, systemic lupus erythematosis and scleroderma." (Office Action at page 2, emphasis added). Since the Office explicitly states that GVHD is not the same as transplant rejection, then the Office cannot properly use Goekjian (which only discloses GVHD treatment) as a reference to establish the obviousness of claims 5 and 15-16 - i.e., the use of 3-(1-methyl-1H-indol-3-yl)-4-[1-{(1-pyridin-2-ylmethyl)-piperidin-4-yl}-1H-indol-3-yl]-pyrrole-2,5-dione (hereinafter "Compound A") or 3-(1-methyl-1H-indol-3-yl)-4-[1-(piperidin-4-yl)-1H-indol-3-yl]-pyrrole-2,5-dione (hereinafter "Compound B") in transplant rejection or the use of Compound A or Compound B to prolong graft survival. For at least this reason, please withdraw the outstanding obviousness-based rejection of claims 5, 15-16 and 20-22.

GVHD, which is an element of claim 17 and its dependents, is not found in Albert or Heath. GVHD is mentioned in Goekjian, but the PKC inhibitor used to treat GVHD in Goekjian, i.e., RO32-0432, is structurally quite different from compounds A and B of the present invention and is conformationally restricted, as noted on page 2131, left column. Moreover, Goekjian notes that the compound was abandoned in development in favor of more selective inhibitors. Goekjian does not therefore motivate the skilled reader to arrive at the present invention. For at

least this reason, Applicants respectfully submit that claims 17-19 are not obvious. Please withdraw the outstanding obviousness-based rejection of claims 17-19.

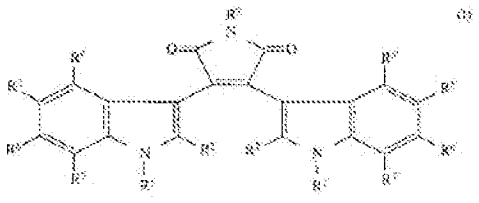
There are additional reasons that the pending claims are patentable over the cited art. One would not be motivated to use a Heath compound to treat transplant rejection or GVHD for the following reasons:

1) the genus of compounds in Heath is very large and there is no motivation to select the two specific compounds recited in Applicants claims;
2) the genus of disorders in Albert is very large and there is no motivation to select the specific disorders recited in Applicants claims;
3) Heath teaches that only certain PKC isoforms are associated with specific disorders;
4) The PKC inhibitors of Heath are specific for PKC beta isoforms, and there is no indication in any of the cited art that PKC beta is associated with transplant rejection, prolongation of graft survival or GVHD;
5) The PKC inhibitor used in Albert to address heart transplant rejection in rats is a PKC alpha inhibitor; and
6) The PKC inhibitor used in Goekjian, RO32-0432, is a selective PKC alpha inhibitor.

As identified in point #1 and #2, above, for the instant claims there are at least two genera from the cited art that one must address for an obviousness determination: 1) the compounds used;[2] and 2) the disorders treated.[3] Moreover, for a proper obviousness analysis, one must consider what the cited art as a whole explicitly states or inherently implies about these genera.

Heath teaches an extremely large genus of PKC inhibitors. (See Heath, Column 2, lines 47 – column 5, line 23). That genus is as follows:

Formula I:

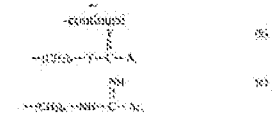


wherein:

R^1 and R^2 are independently hydrogen, alkyl, haloalkyl, alkenyl, arylalkyl, alkoxyalkyl, hydroxyalkyl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, acylaminoalkyl, acyloxyalkyl, cyanoalkyl, amidinoalkyl, carboxyalkyl, alkoxycarbonylalkyl, aminocarbonylalkyl, or a group of the formula:

[2] Allegedly provided by Heath.
[3] Allegedly provided by Albert.

—$(CH_2)_n$—W—Het,



Het signifies a heteroaryl group;

W signifies NH, S or a bond;

T signifies NH or S; V signifies O, S, NH, or NCN;

A signifies alkylthio, amino, monoalkylamino or dialkylamino;

Ar signifies aryl;

R^0 and R^1 are independently hydrogen, alkyl, alkoxyalkyl, hydroxyalkyl, C_1–C_6 alkylthio, $S(O)C_1$–C_6 alkyl, CF_3, or R^1 and R^0 can combine to form —$(CH_2)_s$—X—CH_2—;

R^2 is hydrogen or CH_3CO—;

R^3, R^4, R^5, R^6, R^7, R^8 and R^9 are independently hydrogen, halogen, alkyl, hydroxy, alkoxy, —$COOC_1$–C_6 alkyl), CF_3, nitro, amino, acetylamino, monoalkylamino, dialkylamino, alkylthio, C_1–C_6 alkylthio, or $S(O)C_1$–C_6 alkyl;

X is CHR^3 or NR^3;

R^9 is $(CH_2)_pR^{10}$;

R^{10} is hydrogen, hydroxy, alkoxy, amino, monoalkylamino, dialkylamino, trialkylamino, azido, acylamino, alkoxycarbonyl, cyano, amidino, or aminocarbonyl;

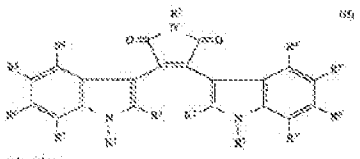
n is 1, 2, 3, 4, 5 or 6;

s is 1, 2, or 3; and

s is 0, 1, 2 or 3.

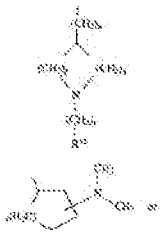
As selective inhibitors, the invention further provides a method for treating diabetes mellitus, which comprises administering to a mammal in need of such treatment a pharmaceutically effective amount of a compound of the Formula I.

In addition, the present invention provides novel compounds, which are isozyme selective PKC inhibitors, of the Formulas II, III, and IV:

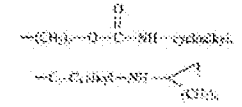


wherein

R^{11} is



R^{11} is



or alkylglycose residue;

R^{12} is hydrogen, C_1–C_6 alkyl, cyclopropylmethyl, aminoalkyl, monoalkylaminoalkyl, or dialkylaminoalkyl;

R^{13} and R^{14} are independently hydrogen, alkyl, alkoxyalkyl, hydroxyalkyl, C_1–C_6 alkylthio, $S(O)C_1$–C_6 alkyl, CF_3;

R^{15} is hydrogen or CH_3CO—;

R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22} and R^{23} are independently hydrogen, halogen, alkyl, hydroxy, alkoxy, —$COOC_1$–C_6 alkyl), CF_3, nitro, amino, acetylamino, monoalkylamino, dialkylamino, alkylthio, C_1–C_6 alkylthio, or $S(O)C_1$–C_6 alkyl;

n is 1, 2, 3, 4, 5 or 6; or

pharmaceutically acceptable salts or solvates thereof.

R^1 is hydrogen, C_1–C_4 alkyl, aminoalkyl, monoalkylaminoalkyl, or dialkylaminoalkyl;

R^2 and R^3 are independently hydrogen, alkyl, alkoxyalkyl, hydroxyalkyl, C_1–C_6 alkylthio, $S(O)C_1$–C_6 alkyl, CF_3;

R^4 is hydrogen or CH_3CO—;

R^5, R^6, R^7, R^8, R^9, R^{10} and R^{11} are independently hydrogen, halogen, alkyl, hydroxy, alkoxy, —$COOC_1$–C_6 alkyl), CF_3, nitro, amino, acetylamino, monoalkylamino, dialkylamino, alkylthio, C_1–C_6 alkylthio, or $S(O)C_1$–C_6 alkyl;

R^{12} is hydrogen, alkyl, haloalkyl, cycloalkyl, benzyl, aryl, —$CH(aryl)_2$, amino, monoalkylamino, dialkylamino, guanidino, —C_1–C_6–N (alkoxycarbonyl) NH_2(alkoxycarbonyl), amidino, hydroxy, carboxy, alkoxycarbonyl or benzoxycarbonyl;

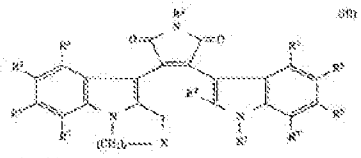
p and q are independently 1, 2, 3, or 4;

s is 0, 1, 2 or3;

t is 1 or 2;

u is 0 or 1; or

pharmaceutically acceptable salts or solvates thereof.



wherein:

R^{13} is hydrogen, C_1–C_6 alkyl, aminoalkyl, monoalkylaminoalkyl, or dialkylaminoalkyl;

R^{14} is hydrogen, alkyl, alkoxyalkyl, hydroxyalkyl, C_1–C_6 alkylthio, $S(O)C_1$–C_6 alkyl, CF_3;

R^{15} is hydrogen or CH_3CO—;

R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22} and R^{23} are independently hydrogen, halogen, alkyl, hydroxy, alkoxy, —$COOC_1$–C_6 alkyl), CF_3, nitro, amino, acetylamino, monoalkylamino, dialkylamino, alkylthio, C_1–C_6 alkylthio, or $S(O)C_1$–C_6 alkyl,

X is $CR^{24}R^{25}$;

R^{24} is $(CH_2)_pR^{26}$;

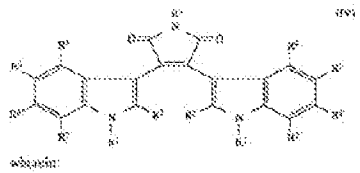
R^{25} is $(CH_2)_qR^{27}$;

R^{26} and R^{27} are independently hydroxy, alkoxy, carboxy, acyloxy, amino, monoalkylamino, dialkylamino, trialkylammonio, azido, acylamino, alkoxycarbonyl, cyano, amidino, or aminocarbonyl;

r is 1, 2, or 3;

s is 0, 1, 2 or 3; or

pharmaceutically acceptable salts or solvates thereof.



wherein:

In addition to this very large genus, Heath teaches that the compounds therein are highly selective inhibitors of the PKC beta 1 and PKC beta 2 isozymes (see, e.g., Heath, Column 2, lines 28-34). Heath warns that that "[o]nly one or two of the protein kinase C isozymes may be involved in a given disease state. For example, the elevated blood glucose levels found in diabetes leading to an isozyme-specific elevation of the beta-2 isozyme in vascular tissues." (Heath, Column 1, lines 45-49). Heath indicates that because of the isozyme selectivity of the disclosed compounds, such compounds are useful in treating disease states associated with an elevation of the beta-1 and beta-2 isozymes. (Heath, Column 2, lines 33-38). Accordingly, Heath teaches that only certain PKC isozymes are associated with certain disorders, which suggest to a skilled artisan that one should exercise care in selecting a PKC inhibitor to treat a desired disorder, namely that one should select a PKC inhibitor that selectively inhibits the associated PKC isozyme.

Albert discloses a large genus of PKC inhibitors and their use to treat a very large genus of disorders. For example, Albert claims that the PKC inhibitors therein are

> useful in the treatment and/or prevention of diseases or disorders mediated by T lymphocytes and/or PKC, e.g. acute or chronic rejection of organ or tissue allo- or xenografts, atherosclerosis, vascular occlusion due to vacular injury such as angioplasty, restenosis, hypertension, heart failure, chronic obstructive pulmonary disease, CNS diseases such as Alzheimer disease or amyotrophic lateral sclerosis, cancer, infectious diseases such as AIDS, septic shock or adult respiratory distress syndrome, ischemia/reperfusion injury e.g. myocardial infarction, stroke, gut ischemia, renal failure or hemorrhage shock, or traumatic shock. The compounds of formula I are also useful in the treatment and/or prevention of T-cell mediated acute or chronic inflammatory diseases or disorders or autoimmune diseases e.g. rheumatoid arthritis, osteoarthritis, systemic lupus erythematosus, Hashimoto's thyroidis, multiple sclerosis, myasthenia gravis, diabetes type I or II and the disorders associated therewith, respiratory diseases such as asthma or inflammatory lung injury, inflammatory liver injury, inflammatory glomerular injury, cutaneous manifestations of immunologically-mediated disorders or illnesses, inflammatory and hyperproliferative skin diseases (such as psoriasis, atopic dermatitis, allergic contact dermatitis, irritant contact dermatitis and further eczematous dermatitises, seborrhoeic dermatitis), inflammatory eye diseases, e.g. Sjoegren's syndrome,

keratoconjunctivitis or uveitis, inflammatory bowel disease, Crohn's disease or ulcerative colitis.

While the Supreme Court in KSR v. Teleflex, 127 S.Ct. 1727 (2007) has rejected the rigidity of the "teaching, suggestion or motivation test" and allows motivation to be found via other avenues – the Office must provide some reason to select portions from a cited reference. Indeed, "there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR Int'l v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) (*quoting In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006). The Office has yet to identify the rational underpinning to select Compound A and Compound B from the very large genus of Heath, to select prevention or treatment of transplant rejection or prolongation of graft survival from Albert, and to combine these selections together. Without such rationale, no obviousness rejection can be maintained. For at least this reason, please withdraw all outstanding obviousness-based rejections. [4]

Albert shows data at [0244] that suggests that the compound of Example 100 is useful for promoting graft survival. However, according to [0228], the compound of Example 100 is a PKC alpha inhibitor. The Office insists that the compounds of Albert are also PKC beta inhibitors (See Office Action at page 4). While this may be true (as a large enough dose of any compound could theoretically inhibit PKC beta), the ONLY compound exemplified by Albert to address *in vivo* transplantation is a PKC alpha inhibitor. No such testing is proved for any PKC beta inhibitor of Albert (even though Albert clearly discloses PKC beta inhibitors in the Examples). The only thing that Albert can be said to teach is that compound 100 may be used to effect graft survival. As for the other compounds and disorders of Albert, Albert does not indicate which PKC isozymes are associated with which disorders. This is of great concern according to Heath because "[o]nly one or two of the protein kinase C isozymes may be involved in a given disease state". Therefore, the Office turns to Goekjian to provide the missing evidence – namely that a PKC beta inhibitor could be used to treat GVHD, prolong graft survival or modulate transplant rejection.

Regarding Goekjian, Table 4 therein shows that RO32-0432 is a PKC alpha inhibitor, having an IC_{50} of 9 nM for PKC alpha and an IC_{50} of between 28-31 nM for PKC beta 1 and 2

[4] The Office notes that Applicants' specification recites Heath as a mode of synthesizing the compounds recited in Applicants' claims. As shown above, Heath provides a very large genus of compounds. While Applicants selected Compound A and Compound B from the genus of Heath, this is not evidence that another would select Compound A and Compound B from Heath. Applicants' disclosure may not be relied upon in the instant obviousness rejection. Such reliance is pure hindsight and is strictly proscribed by the Office and the courts. Thus, it is irrelevant that Applicants' specification recites Heath as a mode of synthesizing the compounds recited in Applicants' claims.

isozymes. Notably, table 4 of Goekjian also analyzes a very selective and strong PKC beta inhibitor – i.e., LY-333531, having an IC_{50} of between 5-6 nM for PKC beta 1 and 2 isozymes (and only 360 nM for PKC alpha). In fact, Goekjian discusses the excellent selectivity of LY-333531 for PKC beta isozymes on page 2131. If, indeed, as the Office alleges on page 3 of the instant Office Action, RO32-0432 is a selective PKC beta inhibitor – why would the Goekjian authors not emphasize this as they did for LY-333531? The Office insists that RO32-0432 would inhibit PKC beta isoforms as well as PKC alpha. While this may be true, as indeed using any compound at a high concentration will non-specifically inactivate various enzymes, the question for an obviousness analysis is what does the art as a whole teach or suggest? *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984) (stating that a prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention).[5] A skilled artisan, viewing Goekjian would understand that RO32-0432 selectively inhibits PKC alpha and that it can be used to treat GVHD, while LY-333531 selectively inhibits PKC beta and that it can be used to treat cancer.

The Office cites Graff et al. (August 15, 2005) to evidence that Compound A of Applicants' claims can inhibit PKC alpha. First, Graff, being published August 15, 2005, may not be properly used to determine what a skilled artisan would understand about Compound A at the time of filing (April 7, 2005) or Applicant's priority date (April, 2004). Second, Graff shows nothing not already established by Heath. That is, Compounds A and B are shown in Examples 49 and 52 of Heath, wherein these compounds have IC_{50}'s for PKC beta-1 and beta-2 isozymes of 0.03 μM. The compound of Example 49 has an IC_{50} for PKC alpha of 0.8 μM, which is about 30 times less sensitive than the effect of said compound on PKC beta isozymes, and the compound of Example 52 has an IC_{50} of 0.3 μM, which is 10 times less sensitive than the effect of said compound on PKC beta isozymes. Again, the question is, what does the art, as a whole teach or suggest? A skilled artisan, viewing Heath would understand that Compound A and Compound B selectively inhibit PKC beta, especially in light of the strong and clear statements in Heath that his compounds are "selective protein kinase C beta-1 and beta-2 isozyme inhibitors." (Heath, Abstract). Heath also warns that "[o]nly one or two of the protein kinase C isozymes may be involved in a given disease state", effectively ensuring that a skilled artisan would very carefully select a PKC inhibitor that would target the PKC isozyme involved in a disorder of interest.

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[5] The MPEP specifically requires the Office to "consider[] both the invention and the prior art references as a whole" and warns of distilling an invention down to a "gist" or "thrust", as such distillation disregards the "as a whole" requirement for an obviousness analysis. *See W.L. Gore*, 721 F.2d 1540 (Fed. Cir. 1983); MPEP § 2141.02.

In light of the art cited by the Office, a skilled artisan would understand:

1) only one or two PKC isozymes may be involved in a given disease state;
2) a PKC alpha inhibitor may be used to increase graft survival;
3) a selective PKC alpha inhibitor may be used to treat GVHD; and
4) Compound A and B are selective PKC beta inhibitors.

Given the above teachings, a skilled artisan would **not** select any PKC beta 1 or 2 inhibitor from Heath for the treatment of organ or tissue transplant rejection, the prophylaxis of graft-versus-host disease or for the prolongation of graft survival. In fact, because Heath emphasizes that only one or two PKC isozymes may be involved in a given disease state, the Heath effectively teaches away from using the selective PKC beta inhibitors therein to treat organ or tissue transplant rejection or GVHD. Moreover, even if one were to ignore the explicit warnings of Heath, why would one have motivation to specifically select Compound A or Compound B from the very large genus of Heath?

In sum, Heath warns that only certain PKC isozymes are associated with different disorders. However, the large list of disorders in Albert is not correlated with specific PKC isozymes. In Albert, only a PKC alpha inhibitor is used to promote graft survival. In Goekjian, only a selective PKC alpha inhibitor is used to treat GVHD. In Heath there is an extremely broad genus of selective inhibitors of PKC beta 1 and beta 2. Accordingly, there is no apparent reason that one of skill in the art would select Compound A or Compound B for use in Applicants' methods. There is simply no evidence that the selective PKC beta-inhibiting compounds of Heath are equivalent to the PKC alpha inhibitors of Albert or Goekjian, such that substitution of one for the other would be routine and obvious. There is even less evidence that a skilled artisan would select Compound A or Compound B from Heath to use in Applicants' methods. Finally, given the warnings of Heath regarding isozyme specificity -- what possible expectation of success could a skilled artisan have in using a PKC beta inhibitor to treat transplant rejection, promote graft survival or treat graft versus host disease? A reasonable expectation of success remains a main element of any proper *prima facie* case of obviousness. Given the teaching of the art, there can be no reasonable expectation of success at arriving at what Applicants have claimed.

For at least these reasons, please withdraw the outstanding obviousness rejection.

CONCLUSION

In view of the foregoing distinctions and remarks, Applicants submit that the presently claimed invention is neither disclosed nor suggested by the cited references, and that all the criteria of 35 U.S.C. §112 are satisfied for the instant application. Accordingly, favorable reconsideration of the application is earnestly solicited.

Please send any further correspondence relating to this application to the undersigned attorney at the address below.

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